Vitamin D Switches BAF Complexes to Protect beta Cells.

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Public Summary:
A primary cause of disease progression in type 2 diabetes (T2D) is beta cell dysfunction due to inflammatory stress and insulin resistance. However, preventing beta cell exhaustion under diabetic conditions is a major therapeutic challenge. Here, we identify the vitamin D receptor (VDR) as a key modulator of inflammation and beta cell survival. Alternative recognition of an acetylated lysine in VDR by bromodomain proteins BRD7 and BRD9 directs association to PBAF and BAF chromatin remodeling complexes, respectively. Mechanistically, ligand promotes VDR association with PBAF to effect genome-wide changes in chromatin accessibility and enhancer landscape, resulting in an anti-inflammatory response. Importantly, pharmacological inhibition of BRD9 promotes PBAF-VDR association to restore beta cell function and ameliorate hyperglycemia in murine T2D models. These studies reveal an unrecognized VDR-dependent transcriptional program underpinning beta cell survival and identifies the VDR:PBAF/BAF association as a potential therapeutic target for T2D.

Scientific Abstract:
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